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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/891,053	06/25/2001	Hiraku Itadani	06501-083001 / B1-103PCT-	9691

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EXAMINER	
ULM, JOHN D	

ART UNIT	PAPER NUMBER
1646	13

DATE MAILED: 02/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/891,053	Itadani et al.
Examiner	**Art Unit**
John Ulm	1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) X Responsive to communication(s) filed on *Nov 12, 2002* .

2a) ☐ This action is **FINAL**. 2b) X This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) X Claim(s) *1-35* is/are pending in the application.

4a) Of the above, claim(s) *8-29 and 32-35* is/are withdrawn from consideration.

5) X Claim(s) *31* is/are allowed.

6) X Claim(s) *1-7 and 30* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s).
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application (PTO-152)
3) X Information Disclosure Statement(s) (PTO-1449) Paper No(s). *7, 9*	6) ☐ Other:

1) Claims 1 to 35 are pending in the instant application.

2) Claims 8 to 29 and 32 to 35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 12, filed 12 November of 2002.

3) The table presented on page 29 of the instant specification does not comply with 37 C.F.R. 1.52 © with respect to font size.

37 C.F.R. 1.58 © states that:

> Chemical and mathematical formulae and tables must be presented in compliance with § 1.52(a) and (b), except that chemical and mathematical formulae or tables may be placed in a landscape orientation if they cannot be presented satisfactorily in a portrait orientation. Typewritten characters used in such formulae and tables must be chosen from a block (nonscript) type font or lettering style **having capital letters which are at least 0.21 cm. (0.08 inch) high** (e.g., elite type). A space at least 0.64 cm. (1/4 inch) high should be provided between complex formulae and tables and the text. Tables should have the lines and columns of data closely spaced to conserve space, consistent with a high degree of legibility.

Correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4) Claim 31 is allowable as written.

5) Claims 1 to 7 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the production and use of an isolated protein comprising the amino acid sequence presented in SEQ ID NO:20 and 25 of the instant

specification or specific portions thereof, it does not reasonably provide an adequate written description of any other polypeptide which functions as a histamine receptor, or the guidance needed to make it. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 1, for example, encompasses any polypeptide having at least 60% sequence identity to either of the two amino acid sequences recited therein wherein that polypeptide functions as a receptor. The instant specification discloses that a polypeptide comprising the amino acid sequence presented in either SEQ ID NO:20 or 25 of the instant specification corresponds to a naturally occurring protein which is a histamine-activated member of the family of proteins known as G protein-coupled receptors. It further discloses that a protein comprising one of the two amino acid sequences presented in SEQ ID NO:20 and 25 can be used to identify ligands which may be potentially pharmacologically relevant. The information derived therefrom, however, is only relevant in so far as it is applicable to a native protein.

Whereas the instant claims potentially encompass ten of thousands of naturally and non-naturally occurring embodiments, the instant specification only describes two working examples and those two examples correspond to two naturally occurring orthologues of a common protein. The instant specification does not provide even one working example of a functional receptor protein of the instant invention whose amino acid sequence deviates from nature by as little as a single amino acid sequence, much less the 180 residues permitted by claim 1. Further, the instant

specification does not identify those amino acid residues in the amino acid sequence of SEQ ID NO:20 or 25 which are essential for the biological activity and structural integrity of a histamine receptor comprising that sequence and those residues which are either expendable or substitutable nor does it identify a structurally related protein in the prior art for which this information is known and could be applied to the claimed protein by analogy. In the absence of such structure-function information a practitioner would have to resort to a substantial amount of undue experimentation in the form of insertional, deletional and substitutional mutation analysis of over 450 amino acid residues before they could even begin to rationally design a functional histamine receptor polypeptide having other than a natural amino acid sequence.

As disclosed in the instant specification, a protein of the instant invention is a member of the G protein-coupled receptor family. By definition, all of the proteins belonging to this family share a complex serpentine structure comprising four extracellular domains, seven transmembrane domains and four cytoplasmic domain. The ligand binding activity of the subfamily of receptors to which the instant invention belongs, which includes adrenergic and dopamine receptors, is generally attributed to interactions between a ligand, various amino acid side chains extending from several different extracellular and transmembrane domains and the hydrophobic pocket formed by those transmembrane domains. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970), held that

> "Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since such improvements

while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and, hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved."

Given the complex structure of a protein of the instant invention, and the lack of working examples and guidance in the predictable alteration of such proteins, and artisan could not reasonably produce a receptor protein of the instant invention whose amino acid sequence deviates from either of those two sequences recited in the claims by even a single amino acid sequence and reasonable "predict by resort to known scientific law" whether that protein will function as a histamine receptor and, more important, whether that protein will perform in a manner that is predictive of a native protein. The only specific and substantial disclosed utility for the claimed protein is in the identification of pharmacologically useful compounds. If a protein which meets all of the current limitations of the instant claims does not function in a manner that is predictive of a native protein in its natural environment then the instant specification fails to disclose how to use that protein.

Further, these claims encompass subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims encompass, for example, a "substantially pure polypeptide comprising an amino acid sequence" "at least 90% identical to SEQ ID NO:20 or 25" wherein said protein "has a G protein-coupled receptor activity". It is a routine matter for an artisan to identify those members of the genus of proteins which meet the first two limitations of being a "substantially pure polypeptide" and "comprising an amino acid sequence" "at least 90% identical to SEQ ID NO:20 or 25". However, one of ordinary skill would not reasonably expect that the majority of proteins belonging to that genus would also meet the limitation "has a G protein-coupled receptor activity". One would not reasonable expect the functional limitation of the instant claims to inherently flow from the structural limitations recited therein. Further, the instant specification does not identify that physical property of combination of physical properties which can be used to distinguish those proteins which meet the functional limitation of the claims from those that don't. The inclusion of a functional limitation in the claims in the absence of a recitation of those material features which provide that function constitutes nothing more than a wish to know the identity of any proteins which meet all of the limitations of the claims. In the decision *The Regents of the University of California v. Eli Lilly and Company,* 43 USPQ2d 1398 (CAFC 1997), the court held that:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc. , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood , 107 F.3d at 1572, 41 USPQ2d at 1966.

Whereas the instant specification provides a detailed description of two naturally occurring proteins which meet all of the limitations of the claims, the instant specification does not provide a written description of the genus of proteins encompassed thereby or even a representative number of the potentially tens of thousands of non-naturally occurring proteins currently claimed.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(e) the invention was described in-
(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

6) Claims 1 to 7 and 30 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by the Goodearl et al. patent (5,882,893, cited by Applicant). The Goodearl et al. patent described an isolated polypeptide comprising the amino acid sequence presented in SEQ ID NO:2 therein, which is identical to the first 445 amino acid residues of SEQ ID NO:20 of the instant application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John D. Ulm whose telephone number is (703) 308-4008. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242 or (703) 872-9306. Official responses under 37 C.F.R. § 1.116 should be directed to (703) 872-9307.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.